

COMPOUNDS AND COMPOSITIONS AS LXR MODULATORS

5 CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application number 60/544,149, filed 11 February 2004. The full disclosure of this application is incorporated herein by reference in its entirety and for all purposes.

BACKGROUND OF THE INVENTION

10 Field of the Invention

[0002] The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of liver X receptors (LXRs).

Background

15 [0003] Liver X receptors (LXRs), LXR α and LXR β , are nuclear receptors that regulate the metabolism of several important lipids, including cholesterol and bile acids. While LXR β is expressed ubiquitously in the body, LXR α is expressed in the liver and to a smaller degree in the kidneys, small intestine, adipose tissue, spleen and adrenal glands.

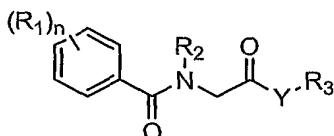
[0004] LXRs bind to the ATP binding cassette transporter-1 (ABCA1) promoter and increase
20 expression of the gene to produce ABCA1 protein. ABCA1 is a membrane bound transport protein that is involved in the regulation of cholesterol efflux from extra-hepatic cells onto nascent high-density lipoprotein (HDL) particles. Mutations in the ABCA1 gene result in low levels of HDL and an accompanying increased risk of cardiovascular diseases such as atherosclerosis, myocardial infarction and ischemic stroke. LXR α and β agonists have been
25 shown to increase ABCA1 gene expression thereby increasing HDL cholesterol and, as a consequence, decreasing both the net absorption of cholesterol and the risk of cardiovascular disease. LXR agonists also upregulate macrophage expression of apolipoprotein E (apoE) and ABCG1, both of which contribute to the efflux of cellular cholesterol. By stimulating macrophage cholesterol efflux through upregulation of ABCA1, ABCG1 and/or apoE expression,

as well as increasing the expression of other target genes including cholesterol ester transfer protein and lipoprotein lipase, LXR agonists influence plasma lipoproteins.

[0005] The novel compounds of this invention modulate the activity of LXRs and are, therefore, expected to be useful in the treatment of LXR-associated diseases such as cardiovascular diseases, inflammation and disorders of glucose metabolism such as insulin resistance and obesity.

SUMMARY OF THE INVENTION

[0006] In one aspect, the present invention provides compounds of Formula I:



[0007] in which:

[0008] Y is selected from O, NR₄ and S; wherein R₄ is selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl, halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl;

[0009] n is selected from 0, 1, 2, 3 and 4;

[0010] R₁ is selected from halo, hydroxy, nitro, cyano, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy, -XC(O)R₄, -XOC(O)R₄, -XC(O)OR₄, -XOR₄, -XS(O)₂R₄, -XS(O)R₄, -XSR₄, -XNR₄R₈, -XC(O)NR₄R₈, -XNR₄C(O)R₄, -XNR₄C(O)OR₄, -XNR₄C(O)NR₄R₈, -XNR₄C(NR₄R₄)NR₄R₈, -XP(O)(OR₄)OR₄, -XOP(O)(OR₄)OR₄, -XS(O)₂NR₄R₈, -XS(O)NR₄R₈, -XSNR₄R₈, -XNR₄S(O)₂R₄, -XNR₄S(O)R₄, -XNR₄SR₄, -XNR₄C(O)NR₄R₈, - and -XC(O)SR₄; wherein X is a bond or C₁₋₆alkylene; and R₄ and R₈ are independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl, halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl; or R₄ and R₈ together with the nitrogen atom to which R₄ and R₈ are attached form C₅₋₁₀heteroaryl or C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₄ or the combination of R₄ and R₈ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy;

[0011] R₂ is selected from C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl; wherein any aryl-alkyl, heteroaryl-alkyl, cycloalkyl-

alkyl or heterocycloalkyl-alkyl of R_2 is optionally substituted by 1 to 5 radicals independently selected from halo, cyano- C_{0-6} alkyl, C_{1-6} alkoxy, halo-substituted- C_{1-6} alkyl, halo-substituted- C_{1-6} alkoxy, $-OXR_7$, $-OXC(O)NR_7R_8$, $-OXC(O)NR_7XC(O)OR_8$, $-OXC(O)NR_7XOR_8$, $-OXC(O)NR_7XNR_7R_8$, $-OXC(O)NR_7XS(O)_{0-2}R_8$, $-OXC(O)NR_7XNR_7C(O)R_8$, $-OXC(O)NR_7XC(O)XC(O)OR_8$, $-OXC(O)NR_7R_9$, $-OXC(O)OR_7$, $-OXOR_7$, $-OXR_9$, $-XR_9$, $-OXC(O)R_9$, $-OXS(O)_{0-2}R_9$ and $-OXC(O)NR_7CR_7[C(O)R_8]_2$; wherein X is a selected from a bond and C_{1-6} alkylene wherein any methylene of X can optionally be replaced with a divalent radical selected from C(O), NR_7 , $S(O)_2$ and O; R_7 and R_8 are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted- C_{1-6} alkyl, halo-substituted- C_{1-6} alkoxy, C_{6-10} aryl- C_{0-4} alkyl, C_{3-8} heteroaryl- C_{0-4} alkyl, C_{3-12} cycloalkyl- C_{0-4} alkyl and C_{3-8} heterocycloalkyl- C_{0-4} alkyl; R_9 is selected from C_{6-10} aryl- C_{0-4} alkyl, C_{5-10} heteroaryl- C_{0-4} alkyl, C_{3-12} cycloalkyl- C_{0-4} alkyl and C_{3-8} heterocycloalkyl- C_{0-4} alkyl; wherein any alkyl of R_9 can have a hydrogen replaced with $-C(O)OR_{10}$; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_7 , R_8 or R_9 is optionally substituted with 1 to 4 radicals independently selected from halo, cyano, hydroxy, C_{1-6} alkyl, C_{3-12} cycloalkyl, halo-substituted- C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted- C_{1-6} alkoxy, $-XC(O)OR_{10}$, $-XOR_{10}$, $-XR_{11}$, $-XOR_{11}$, $-XC(O)R_{11}$, $-XNR_{10}C(O)OR_{10}$, $-XNR_{10}C(O)R_{10}$, $-XNR_{10}S(O)_{0-2}R_{10}$, $-XS(O)_{0-2}R_{11}$, $-XC(O)R_{10}$, $-XC(O)NR_{10}R_{11}$, $-XC(O)NR_{10}OR_{10}$, $-XC(O)NR_{10}R_{10}$, $-XS(O)_{0-2}NR_{10}R_{10}$ and $-XS(O)_{0-2}R_{10}$; wherein R_{10} is independently selected from hydrogen, C_{1-6} alkyl and halo-substituted- C_{1-6} alkyl; and R_{11} is independently selected from C_{6-10} aryl, C_{3-8} heteroaryl, C_{3-12} cycloalkyl and C_{3-8} heterocycloalkyl;

[0012] R_3 is selected from C_{1-10} alkyl, C_{1-10} alkoxy, halo-substituted- C_{1-10} alkyl, halo-substituted- C_{1-10} alkoxy and C_{3-12} cycloalkyl optionally substituted with 1 to 3 C_{1-6} alkyl radicals; and the N-oxide derivatives, S-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

[0013] In a second aspect, the present invention provides a pharmaceutical composition which contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients. In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of LXR activity can prevent, inhibit or ameliorate the pathology and/or symptomatology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

[0014] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which LXR activity contributes to the pathology and/or symptomatology of the disease.

[0015] In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual
5 isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0016] "Alkyl" as a group and as a structural element of other groups, for example halo-
10 substituted-alkyl and alkoxy, can be either straight-chained or branched. C₁₋₆alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

[0017] "Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl can be phenyl or naphthyl, preferably phenyl.
15 "Arylene" means a divalent radical derived from an aryl group. "Heteroaryl" is as defined for aryl where one or more of the ring members are a heteroatom. For example heteroaryl includes pyridyl, indolyl, indazolyl, quinoxaliny, quinoliny, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc. "C₆₋₁₀arylC₀₋₄alkyl" means an
20 aryl as described above connected via a alkylene grouping. For example, C₆₋₁₀arylC₀₋₄alkyl includes phenethyl, benzyl, etc.

[0018] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C₃₋₁₀cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.
25 "Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O)-, -S-, -S(O)- or -S(O)₂-, wherein R is hydrogen, C₁₋₄alkyl or a nitrogen protecting group. For example, C₃₋₈heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-
30 8-yl, etc.

[0019] "Halogen" (or halo) preferably represents chloro or fluoro, but can also be bromo or iodo.

[0020] The term "modulate" with respect to an LXR receptor refers to activation of the LXR receptor and its biological activities associated with the LXR pathway (e.g., transcription regulation of a target gene). Modulation of LXR receptor can be up-regulation (i.e., agonizing, activation or stimulation) or down-regulation (i.e. antagonizing, inhibition or suppression). The mode of action of an LXR modulator can be direct, e.g., through binding to the LXR receptor as a ligand. The modulation can also be indirect, e.g., through binding to and/or modifying another molecule which otherwise binds to and activates the LXR receptor. Thus, modulation of LXR includes a change in the bioactivities of an LXR agonist ligand (i.e., its activity in binding to and/or activating an LXR receptor) or a change in the cellular level of the ligand.

[0021] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

[0022] The present invention provides compounds, compositions and methods for the treatment of diseases in which modulation of LXR activity can prevent, inhibit or ameliorate the pathology and/or symptomatology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I.

[0023] In one embodiment, with reference to compounds of Formula I, n is selected from 0, 1, 2 and 3.

[0024] In another embodiment, R₁ is selected from halo, C₁₋₆alkyl and halo-substituted-C₁₋₆alkyl.

[0025] In another embodiment, R₂ is selected from C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl and C₃₋₁₂cycloalkyl-C₀₋₄alkyl; wherein any aryl-alkyl, heteroaryl-alkyl or cycloalkyl-alkyl of R₂ is optionally substituted by 1 to 3 radicals independently selected from halo, hydroxyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl, halo-substituted-C₁₋₆alkoxy, -OXR₇, -OXC(O)NR₇R₈, -OXC(O)NR₇XC(O)OR₈, -OXC(O)NR₇XOR₈, -OXC(O)NR₇XNR₇R₈, -OXC(O)NR₇XS(O)₀₋₂R₈, -OXC(O)NR₇XNR₇C(O)R₈, -OXC(O)NR₇XC(O)XC(O)OR₈, -OXC(O)NR₇R₉, -OXC(O)OR₇, -OXOR₇, -OXR₉, -XR₉, -OXC(O)R₉ and -OXC(O)NR₇CR₇[C(O)R₈]₂; wherein X is a selected from a bond and C₁₋₆alkylene; R₇ and R₈ are independently selected from hydrogen, cyano, C₁₋

alkyl, halo-substituted-C₁₋₆alkyl, C₂₋₆alkenyl and C₃₋₁₂cycloalkyl-C₀₋₄alkyl; R₉ is selected from C₆₋₁₀aryl-C₀₋₄alkyl, C₅₋₁₀heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl; wherein any alkyl of R₉ can have a hydrogen replaced with -C(O)OR₁₀; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₉ is optionally substituted with 1 to 4 radicals
 5 independently selected from halo, C₁₋₆alkyl, C₃₋₁₂cycloalkyl, halo-substituted-C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkoxy, -XC(O)OR₁₀, -XC(O)R₁₀, -XC(O)NR₁₀R₁₀, -XS(O)₀₋₂NR₁₀R₁₀ and -XS(O)₀₋₂R₁₀; wherein R₁₀ is independently selected from hydrogen and C₁₋₆alkyl; and R₃ is selected from C₁₋₁₀alkyl and C₃₋₁₂cycloalkyl optionally substituted with 1 to 3 C₁₋₆alkyl radicals.

10 **[0026]** In another embodiment, R₁ is selected from halo, methyl, ethyl and trifluoromethyl; and R₃ is selected from *t*-butyl, methyl-cyclopentyl, 1,1-dimethyl-propyl, 1-ethyl-1-methyl-propyl and methyl-cyclohexyl.

[0027] In a further embodiment, R₂ is selected from phenyl, benzo[1,3]dioxolyl, cyclopentyl, benzoxazolyl, benzthiazolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3-dihydro-benzofuran, 1H-
 15 indazolyl, 1H-indolyl, naphthyl and 2-oxo-2,3-dihydro-1H-indol-5-yl; wherein any aryl-alkyl, heteroaryl-alkyl or cycloalkyl-alkyl of R₂ is optionally substituted by 1 to 3 radicals selected from halo, hydroxy, methoxy, trifluoro-methoxy, difluoro-methoxy, ethenyl, methyl-sulfanyl, methyl-carbonyl-amino, formamidyl, trifluoro-methyl, methyl, phenyl, oxazolyl, pyrazolyl, pyrrolidinyl-carbonyl, phenoxy, phenyl-carbonyl, pyridinyl, 1H-indolyl, pyrimidinyl, amino-carbonyl,
 20 dimethyl-amino, thiophenyl, methyl-sulphanyl, methyl-formamidyl, methyl-carbonyl, ethenyl, phenoxy, methoxy-carbonyl, benzoxy, isopropyl, furanyl, isopropoxy, [1,3]dioxolanyl and cyano-methyl; wherein any aryl, heteroaryl or heterocycloalkyl substituent of R₂ is optionally substituted by 1 to 3 radicals selected from halo, methyl, cyano, carboxy, carboxy-methyl, cyano-methyl, methoxy, carbonyl-methyl, ethyl, trifluoro-methyl, hydroxy, isopropyl, methyl-sulfonyl-amino,
 25 dimethyl-amino-carbonyl, dimethyl-amino, amino-sulfonyl, chloro-methyl-carbonyl-amino, diethyl-amino-carbonyl, 1-oxo-1,3-dihydro-isobenzofuran-5-yl, 4-oxo-piperidin-1-yl-carbonyl, benzyl-formamidyl, morpholino-carbonyl, cyclopropyl-formamidyl, isobutyl-formamidyl, ethyl-formamidyl, butoxy, ethoxy, benzyl, cyclopentyl-formamidyl, 2-methoxy-propionyl, methoxy-methyl-amino-carbonyl, methyl-carbonyl-amino, 2-oxo-piperidin-1-yl butyl,
 30 *t*-butyl, methyl-sulfonyl-amino, methoxy-methyl, benzo-amino-carbonyl, methoxy-carbonyl, methoxy-carbonyl-ethyl, ethoxy-carbonyl, ethoxy-carbonyl-methyl, phenoxy, hydroxy-methyl, *t*-

butoxy-carbonyl, t-butoxy-carbonyl-amino, phenyl-sulfonyl, phenyl, acetyl-amino, methyl-sulfonyl, methoxy-carbonyl-amino, 1-carboxy-ethyl and trifluoro-methoxy.

[0028] Preferred compounds of Formula I are detailed in the Examples and Table I, *infra*.

Pharmacology and Utility

5 [0029] Compounds of the invention modulate the activity of LXRs and, as such, are useful for treating diseases or disorders in which LXRs contribute to the pathology and/or symptomatology of the disease. This invention further provides compounds of this invention for use in the preparation of medicaments for the treatment of diseases or disorders in which LXRs contribute to the pathology and/or symptomatology of the disease. LXR mediated
10 diseases or conditions include inflammation, cardiovascular disease including atherosclerosis, arteriosclerosis, hypercholesteremia, hyperlipidemia and disorders of glucose homeostasis, including insulin resistance, type II diabetes, and obesity.

[0030] Lipoprotein metabolism is a dynamic process comprised of the production of triglyceride and cholesterol rich particles from the liver as very low-density lipoprotein
15 (VLDL), modification of these lipoprotein particles within the plasma (VLDL to intermediate density (IDL) to low-density lipoprotein (LDL)) and clearance of the particles from the plasma, again by the liver. This process provides the transport of triglycerides and free cholesterol to cells of the body. Reverse cholesterol transport is the proposed mechanism by which excess cholesterol is returned to the liver from extra-hepatic tissue.

20 [0031] The process is carried out by high-density lipoprotein (HDL) cholesterol. The combination of lipoprotein production (VLDL, HDL) from the liver, modification of particles (all) within the plasma and subsequent clearance back to the liver, accounts for the steady state cholesterol concentration in plasma. Compounds of this invention increase reverse cholesterol transport by increasing cholesterol efflux from the arteries. This invention
25 includes the use of compounds of this invention for the preparation of a medicament for increasing reverse cholesterol transport. Additionally, this invention provides compounds for inhibiting cholesterol absorption and the use of compounds of this invention for the preparation of a medicament for inhibiting net cholesterol absorption.

[0032] The compounds of this invention can also be useful for the prevention or treatment
30 of inflammation and neurodegenerative diseases or neurological disorders. Accordingly, this

invention also provides a method for preventing or treating inflammation and a method for preventing or treating neurodegenerative diseases or neurological disorders, particularly neurodegenerative diseases or disorders characterized by neuron degeneration, neuron injury or impaired plasticity or inflammation in the CNS. Particular diseases or conditions that are characterized by neuron degeneration, inflammation, cholesterol and lipid abnormalities in the brain and thus benefiting from the growth and/or repair of neurons include stroke, Alzheimer's disease, fronto-temporal dementias (tauopathies), peripheral neuropathy, Parkinson's disease, dementia with Lewy bodies, Huntington's disease, amyotrophic lateral sclerosis and multiple sclerosis and Niemann-Pick disease. Diseases or conditions that are characterized by neuron degeneration and/or impaired plasticity include psychiatric disorders such as schizophrenia and depression. Particular diseases or conditions that are characterized by neuronal injury include those conditions associated with brain and/or spinal cord injury, including trauma. In addition, the compounds of this invention can be used to treat or prevent various diseases with an inflammatory component, such as rheumatoid arthritis, osteoarthritis, psoriasis, asthma, etc.

[0033] LXR agonists improve glucose tolerance and enhance glut4 expression (U.S. Provisional Patent Application 60/436,112, filed 12/23/2002; U. S. Patent Application 10/745,334, filed 12/22/2003). There is a coordinated regulation of genes involved in glucose metabolism in liver and adipose tissue. In the liver, LXR agonists inhibit expression of several genes that are important for hepatic gluconeogenesis, e.g., PGC-1 α , phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase expression. Inhibition of these gluconeogenic genes is accompanied by an induction in expression of glucokinase, which promotes hepatic glucose utilization. It was also found that glut4 mRNA levels were upregulated by LXR agonists in adipose tissue, and that glucose uptake in 3T3-L1 adipocytes was enhanced in vitro.

[0034] In accordance with these discoveries, the present invention provides methods for enhancing glut4 expression in cells in a subject by administering a compound of the invention to the subject. The present invention also provides methods for treating diabetes mellitus and related disorders, such as obesity or hyperglycemia, by administering to a subject an effective amount of a compound of the invention to ameliorate the symptoms of the disease. For example, type II diabetes is amenable to treatment with methods of the

present invention. By enhancing sensitivity to insulin and glucose uptake by cells, administration with a compound of the invention can also treat other diseases characterized by insulin dysfunction (e.g., resistance, inactivity or deficiency) and/or insufficient glucose transport into cells.

5 [0035] Compounds of the present invention also regulate expression levels of a number of genes that play important roles in liver gluconeogenesis. Accordingly, the present invention further provides methods for reducing gluconeogenesis in a subject by modulating expression of such genes (e.g., PGC-1 and PEPCK).

10 [0036] In the pancreas, LXR activation stimulates insulin secretion via modulation of glucose and lipid metabolism in pancreatic β -cells, suggesting another mechanism for LXR's anti-diabetic effects. LXR modulators can thus also regulate glucose tolerance by enhancing insulin secretion from the pancreas.

[0037] In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need
15 of such treatment, which method comprises administering to said subject a therapeutically effective amount (See, "*Administration and Pharmaceutical Compositions*", *infra*) of a compound of Formula I or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

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Administration and Pharmaceutical Compositions

[0038] In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount can vary
25 widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, conveniently administered, e.g. in divided doses up to four times a day or in retard

form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50mg active ingredient.

[0039] Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions can be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they can also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present invention with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations can also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0040] Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations). For example, synergistic effects can occur with other substances used in the treatment of cardiovascular, inflammatory and/or neurodegenerative diseases. Examples of such compounds include fibrates, TZDs, metformin, etc. Where the compounds of the invention are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

[0041] The invention also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

[0042] The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

[0043] The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Processes for Making Compounds of the Invention

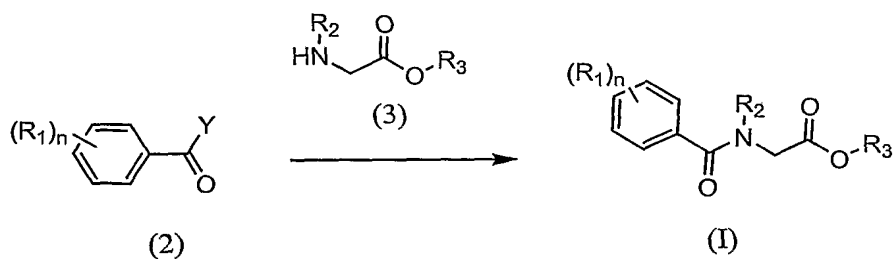
[0044] The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups

can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

[0045] Compounds of Formula I can be prepared by proceeding as in the following Reaction Scheme I:

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Reactions Scheme I



[0046] in which N, R₁, R₂ and R₃ are as defined for Formula I in the Summary of the Invention. Compounds of Formula I are prepared by reacting a compound of formula 2 with a compound of formula 3 in the presence of a suitable solvent (e.g., dichloromethane, or the like) and a suitable base (e.g., diisopropylethylamine, or the like). The reaction is carried out in the temperature range of 10 to 40°C and takes up to 20 hours to complete.

Additional Processes for Making Compounds of the Invention

[0047] A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

[0048] The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

[0049] Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

[0050] Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[0051] Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[0052] Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0053] Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. Resolution of the racemic mixture may be carried out using chiral HPLC. A more detailed description of

the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

[0054] In summary, the compounds of Formula I can be made by a process, which involves:

5 [0055] (a) that of reaction scheme I;

[0056] (b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

[0057] (c) optionally converting a salt form of a compound of the invention to a non-salt form;

10 [0058] (d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

[0059] (e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

15 [0060] (f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

[0061] (g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative;

[0062] (h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

20 [0063] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

[0064] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that

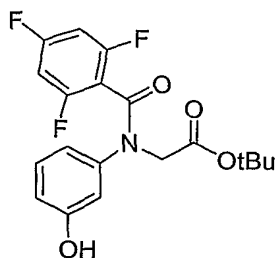
25 other well known methods can similarly be used.

Examples

[0065] The present invention is further exemplified, but not limited, by the following examples that illustrate the preparation of compounds of Formula I according to the invention.

Example 1

30 Tert-butyl 2-(2,4,6-trifluoro-N-(3-hydroxyphenyl)benzamido)acetate

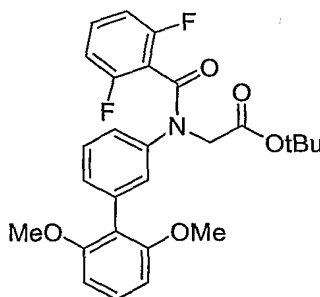


[0066] To a solution of 3-aminophenol (4.58 mmol) in DMF (15 mL) is added N,N-diisopropylethyl amine (4.58 mmol) and *tert*-butylbromoacetate (4.58 mmol) and the reaction mixture is stirred at 50 °C for 2 hours. Ethyl acetate and water are added to the reaction mixture and the phases are separated. The organic phase is dried on sodium sulfate, filtered and the solvent evaporated. The *tert*-butyl 2-(3-hydroxyphenylamino) acetate obtained is used as such in the next step without further purification.

[0067] To a solution in CH₂Cl₂ (15 mL) of *tert*-butyl 2-(3-hydroxyphenylamino)acetate obtained in the previous step, is added N,N-diisopropylethyl amine (9.16 mmol) followed by dropwise addition of 2,4,6-trifluorobenzoyl chloride (9.16 mmol). The reaction mixture is stirred for 12 hours at room temperature. After concentration and redissolution in DMSO, the residue is purified by preparative LCMS (10 to 90% CH₃CN) to give *tert*-butyl 2-(2,4,6-trifluoro-N-(3-hydroxyphenyl)benzamido)acetate: ¹H NMR (400 MHz, CDCl₃) δ 7.06 (t, J = 8.4 Hz, 1H), 6.78 (s, 2H), 6.69 (d, J = 8 Hz, 1H), 6.48 (t, J = 8 Hz, 2H), 5.85 (bs, 1H), 4.42 (s, 2H), 1.49 (s, 9H); MS: (ES⁺) 382.1 (M+1)⁺.

Example 2

Tert-butyl 2-(N-(3-(2,6-dimethoxyphenyl)phenyl)-2,6-difluorobenzamido)acetate



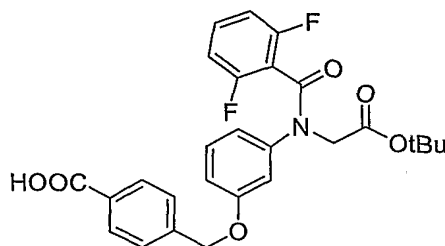
[0068] To a solution of 3-bromoaniline (69.8 mmol) in 200 mL of CH₂Cl₂ under nitrogen atmosphere, is added N,N-diisopropylethyl amine (69.8 mmol) followed by dropwise addition of 2,6-difluorobenzoylchloride (69.8 mmol). The reaction mixture is stirred at room temperature for 5 hours. TLC (hexanes: ethyl acetate = 8:2) and analytical LCMS (20 to 100% CH₃CN) reveal the complete conversion of the starting material to the product. Water is added to the reaction mixture and the phases are separated. The organic layer is dried on sodium sulfate, filtered and the solvent is evaporated. The product, N-(3-bromophenyl)-2,6-difluorobenzamide, is used without further purification in the next step.

[0069] To a solution of N-(3-bromophenyl)-2,6-difluorobenzamide in 200 mL of DMF at room temperature and under nitrogen atmosphere, NaH 60% in oil dispersion (104.7 mmol) is slowly added and the reaction mixture is stirred for 30 minutes. *Tert*-butylbromoacetate (104.7 mmol) is added and the reaction stirred at room temperature. After 12 hours the reaction is complete by TLC (hexanes: ethyl acetate = 8: 2) and analytical LCMS (20 to 100% CH₃CN). Ethyl acetate and water are added to the reaction mixture and the phases are separated. The organic phase is dried on sodium sulfate, filtered and the solvent is evaporated. The crude is purified by automated column chromatography (gradient of hexanes and ethyl acetate) to give *tert*-butyl 2-(N-(3-bromophenyl)-2,6-difluorobenzamido)acetate: ¹H NMR (400 MHz, CDCl₃) δ 7.36 (bs, 1H), 7.20 (m, 1H), 7.07(m, 2H), 6.96 (t, J = 8 Hz, 1H), 6.62 (td, J₁ = 8 Hz, J₂ = 1.2 Hz), 4.32 (s, 2H), 1.39 (s, 9H); MS: (ES⁺) 448.0 (M+23)⁺.

[0070] *Tert*-butyl 2-(N-(3-bromophenyl)-2,6-difluorobenzamido)acetate (0.55 mmol) is mixed with 2,6-dimethoxyphenyl boronic acid (6.13 mmol) and Pd(Ph₃P)₄ (0.024 mmol). To the solid mixture under nitrogen, Na₂CO₃ 2M (0.83 mL) is added followed by DMF (5.6 mL). The reaction mixture is stirred at room temperature for 1 hour and then heated at 85°C for 12 hours. The reaction mixture is purified by automated column chromatography (gradient of hexanes and ethyl acetate) to give *tert*-butyl 2-(N-(3-(2,6-dimethoxyphenyl)phenyl)-2,6-difluorobenzamido)acetate: ¹H NMR (400 MHz, CDCl₃) δ 7.19 (m, 6H), 6.69 (t, J = 7.2 Hz, 2H), 6.58 (d, J = 8.4 Hz, 2H), 4.46 (s, 2H), 3.64 (s, 6H), 1.48 (s, 9H); MS: (ES⁺) 484.1 (M+23)⁺.

Example 3

Tert-butyl 2-(2,6-difluoro-N-(3-(4-carboxybenzyloxy)phenyl)benzamido)acetate



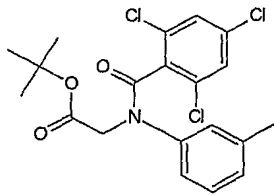
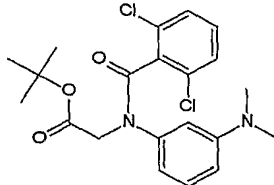
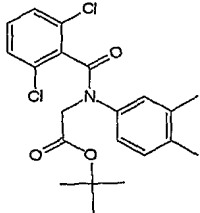
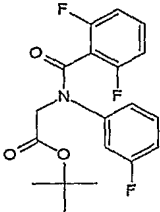
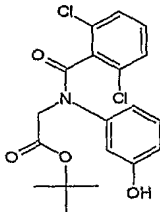
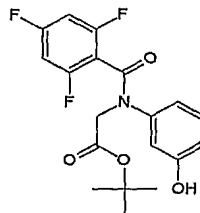
[0071] To a solution of 3-aminophenol (6.98 mmol) in 20 mL of CH_2Cl_2 under nitrogen atmosphere, is added *N,N*-diisopropylethyl amine (6.98 mmol) followed by dropwise addition of 2,6-difluorobenzoylchloride (6.98 mmol). The reaction mixture is stirred at room temperature for 5 hours and the product 2,6-difluoro-*N*-(3-hydroxyphenyl)benzamide is purified by preparative HPLC: ^1H NMR (400 MHz, DMSO) δ 10.68 (s, 1H), 9.55 (bs, 1H), 7.57 (m, 1H), 7.28 (m, 1H), 7.23 (m, 2H), 7.12 (t, $J = 8$ Hz, 1H), 7.05 (m, 1H), 6.54 (m, 1H).

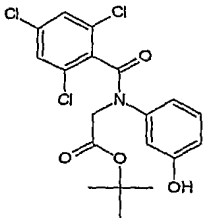
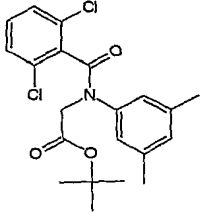
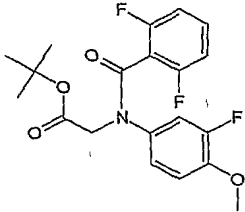
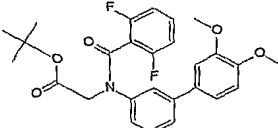
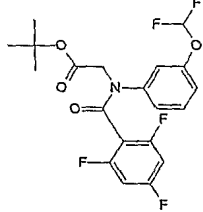
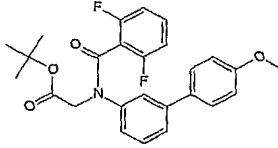
[0072] A solution of 2,6-difluoro-*N*-(3-hydroxyphenyl)benzamide (0.9 mmol) in 4 mL of CH_3CN is treated with potassium carbonate (1.36 mmol) and methyl 4-(bromomethyl)benzoate. The reaction mixture is heated at 80°C for 48 hours. The solvent is evaporated and the O-alkylated product 2,6-difluoro-*N*-(3-(4-carbomethoxybenzyloxy)phenyl)benzamide is obtained after purification with automated column chromatography (gradient of hexanes and ethyl acetate).

[0073] To a solution of 2,6-difluoro-*N*-(3-(4-carbomethoxybenzyloxy)phenyl) benzamide (0.61 mmol) in 4 mL of DMF, first NaH 60% in oil dispersion (0.73 mmol) and after 30 minutes *tert*-butylbromoacetate (0.67 mmol) are added. The reaction is stirred at room temperature for 12 hours. LCMS analysis (10 to 90% CH_3CN) of the reaction mixture reveals that the reaction is complete. DMF is evaporated and the crude *tert*-butyl 2-(2,6-difluoro-*N*-(3-(4-carbomethoxybenzyloxy)phenyl)benzamido)acetate is finally dissolved in 4 mL of MeOH and treated with LiOH 3M (1.95 mmol). The reaction mixture is purified by preparative LCMS (10 to 90% CH_3CN) to give *tert*-butyl 2-(2,6-difluoro-*N*-(3-(4-carboxybenzyloxy)phenyl)-benzamido)acetate: ^1H NMR (400 MHz, CDCl_3) δ 8.12 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.13 (m, 2H), 6.91 (m, 2H), 6.81 (m, 1H), 6.70 (m, 2H), 5.05 (s, 2H), 4.45 (s, 2H), 1.51 (s, 9H); MS: (ES^+) 498.1 ($\text{M}+1$) $^+$.

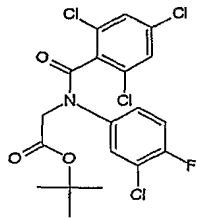
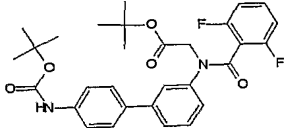
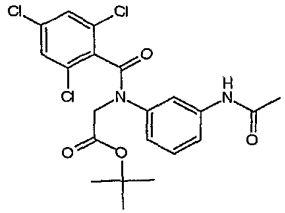
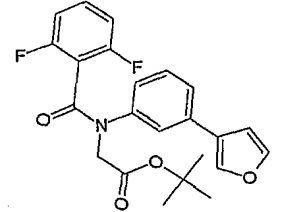
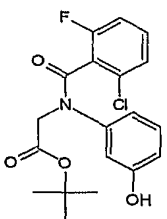
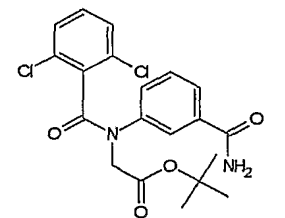
[0074] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1 and Table 2, are obtained.

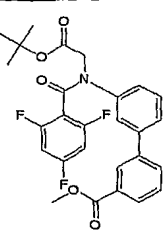
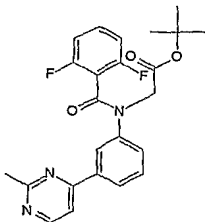
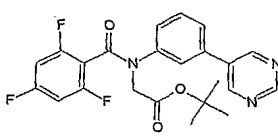
Table 1

Compound number	Structure	MS (m/z) (M+1) ⁺	NMR
4		428.0	¹ H NMR (400 MHz, CDCl ₃) δ 6.88 (m, 6H), 4.23 (s, 2H), 2.02 (s, 3H), 1.26 (s, 9H).
5		423.1	¹ H NMR (400 MHz, CDCl ₃) δ 6.93 (d, J = 1.6 Hz, 2H), 6.85 (m, 2H), 6.61 (m, 2H), 6.32 (m, 1H), 4.29 (s, 2H), 2.65 (s, 6H), 1.31 (s, 9H).
6		408.1	¹ H NMR (400 MHz, CDCl ₃) δ 7.05 (m, 5H), 6.84 (d, J = 8 Hz, 1H), 4.39 (s, 2H), 2.05 (s, 6H), 1.42 (s, 9H).
7		366.1	¹ H NMR (400 MHz, CDCl ₃) δ 7.05 (m, 6H), 6.73 (m, 1H), 4.45 (s, 2H), 1.56 (s, 9H).
8		396.1	¹ H NMR (400 MHz, CDCl ₃) δ 7.06 (m, 6H), 6.6 (m, 1H), 4.48 (s, 2H), 1.50 (s, 9H).
9		382.1	¹ H NMR (400 MHz, CDCl ₃) δ 7.06 (t, J = 8.4 Hz, 1H), 6.78 (s, 2H), 6.69 (d, J = 8 Hz, 1H), 6.48 (t, J = 8 Hz, 2H), 5.85 (bs, 1H), 4.42 (s, 2H), 1.49 (s, 9H).

Compound number	Structure	MS (m/z) (M+1) ⁺	NMR
10		430.0	¹ H NMR (400 MHz, CDCl ₃) δ 7.07 (s, 2H), 6.95 (m, 3H), 6.62 (m, 1H), 4.37 (s, 2H), 1.42 (s, 9H).
11		408.1	¹ H NMR (400 MHz, CDCl ₃) δ 7.18 (s, 1H), 7.04 (d, J = 1.6 Hz, 1H), 6.98 (s, 2H), 6.96 (d, J = 2.4 Hz, 1H), 6.71 (s, 1H), 4.40 (s, 2H), 2.10 (s, 6H), 1.43 (s, 9H).
12		418.1 (M+23) ⁺	¹ H NMR (400 MHz, CDCl ₃) δ 7.19 (m, 1H), 7.1 (m, 2H), 6.78 (m, 3H), 4.41 (s, 2H), 3.81 (s, 3H), 1.51 (s, 9H).
13		484.1	¹ H NMR (400 MHz, CDCl ₃) δ 7.19 (m, 6H), 6.69 (t, J = 7.2 Hz, 2H), 6.58 (d, J = 8.4 Hz, 2H), 4.46 (s, 2H), 3.64 (s, 6H), 1.48 (s, 9H).
14		454.1 (M+23) ⁺	¹ H NMR (400 MHz, CDCl ₃) δ 7.25 (t, J = 8.4 Hz, 1H), 7.14 (m, 2H), 6.99 (dd, J ₁ = 1.6 Hz, J ₂ = 8.4 Hz, 1H), 6.53 (m, 2H), 6.41 (t, J ₁ = 73.2 Hz, 1H), 4.44 (s, 2H), 1.52 (s, 9H).
15		454.1	¹ H NMR (400 MHz, CDCl ₃) δ 7.36 (s, 1H), 7.23 (m, 3H), 7.11 (m, 3H), 6.82 (d, J = 8.8 Hz, 2H), 6.59 (t, J = 7.2 Hz, 2H), 4.38 (s, 2H), 3.72 (s, 3H), 1.39 (s, 9H).

Compound number	Structure	MS (m/z) (M+1) ⁺	NMR
16		490.1 (M+23) ⁺	¹ H NMR (400 MHz, CDCl ₃) δ 7.39 (d, J = 7.6 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.23 (m, 4H), 7.13 (m, 2H), 6.94 (d, J = 7.6 Hz, 1H), 6.65 (t, J = 7.6 Hz, 2H), 4.41 (s, 2H), 4.04 (s, 2H), 3.15 (s, 3H), 1.4 (s, 9H).
17		484.1	¹ H NMR (400 MHz, CDCl ₃) δ 7.49 (s, 1H), 7.36 (m, 1H), 7.26 (m, 3H), 6.98 (dd, J = 2 Hz, 1H), 6.91 (m, 2H), 6.72 (m, 2H), 4.51 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 1.52 (s, 9H).
18		556.2 (M+23) ⁺	¹ H NMR (400 MHz, CDCl ₃) δ 7.49 (s, 1H), 7.43 (m, 5H), 7.29 (t, J = 7.6 Hz, 1H), 7.23 (m, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.07 (m, 4H), 6.52 (m, 2H), 4.49 (s, 2H), 1.52 (s, 9H).
19		494.1 (M+23) ⁺	¹ H NMR (400 MHz, CDCl ₃) δ 7.53 (d, J = 5.6 Hz, 1H), 7.22 (m, 6H), 6.89 (dd, J ₁ = 7.6 Hz, J ₂ = 1.2 Hz, 1H), 6.31 (m, 2H), 4.29 (s, 2H), 4.2 (s, 2H), 1.29 (s, 9H).
20		494.1 (M+23) ⁺	¹ H NMR (400 MHz, CDCl ₃) δ 7.53 (d, J = 7.2 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.36 (m, 5H), 6.53 (t, J = 8.8 Hz, 2H), 4.49 (s, 2H), 4.40 (s, 2H), 1.49 (s, 9H).
21		476.1 (M+23) ⁺	¹ H NMR (400 MHz, CDCl ₃) δ 7.53 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.35 (m, 4H), 7.22 (m, 2H), 7.07 (d, J = 7.6 Hz, 1H), 6.76 (t, J = 7.6 Hz, 2H), 4.51 (s, 2H), 4.36 (s, 2H), 1.5 (s, 9H).

Compound number	Structure	MS (m/z) (M+1) ⁺	NMR
22		466.0	¹ H NMR (400 MHz, CDCl ₃) δ 7.59 (m, 1H), 7.37 (m, 1H), 7.19 (s, 2H), 6.99 (t, J = 8.8 Hz, 1H), 4.44 (s, 2H), 1.49 (s, 9H).
23		539.2	¹ H NMR (400 MHz, CDCl ₃) δ 7.63 (s, 1H), 7.4 (m, 8H), 6.87 (m, 2H), 6.70 (s, 1H), 4.66 (s, 2H), 1.68 (s, 9H), 1.67 (s, 9H).
24		471.0	¹ H NMR (400 MHz, CDCl ₃) δ 7.66 (s, 1H), 7.40 (m, 1H), 7.33 (s, 1H), 7.15 (m, 1H), 7.14 (s, 2H), 4.47 (s, 2H), 2.15 (s, 3H), 1.49 (s, 9H).
25		414.1	¹ H NMR (400 MHz, CDCl ₃) δ 7.71 (s, 1H), 7.53 (t, J = 1.6 Hz, 1H), 7.36 (s, 1H), 7.33 (m, 4H), 6.79 (m, 2H), 6.65 (m, 1H), 4.57 (s, 2H), 1.59 (s, 9H).
26		380.1	¹ H NMR (400 MHz, CDCl ₃) δ 7.81 (m, 1H), 7.68 (m, 1H), 7.55 (m, 2H), 7.42 (m, 2H), 7.20 (m, 1H), 5.04 (d, J = 16.8 Hz, 1H), 4.95 (d, J = 16.8 Hz, 1H), 2.07 (s, 9H).
27		445 (M+23) ⁺	¹ H NMR (400 MHz, CDCl ₃) δ 7.86 (t, J = 1.6 Hz, 1H), 7.58 (m, 2H), 7.23 (t, J = 8 Hz, 1H), 7.01 (m, 3H), 5.95 (bs, 1H), 5.62 (bs, 1H), 4.46 (s, 2H), 1.41 (s, 9H).

Compound number	Structure	MS (m/z) (M+1) ⁺	NMR
28		444.1 (M-55) ⁺	¹ H NMR (400 MHz, CDCl ₃) δ 8.09 (s, 1H), 8.07 (d, <i>J</i> = 7.6 Hz, 1H), 7.63 (d, <i>J</i> = 8 Hz, 1H), 7.53 (m, 3H), 7.34 (t, <i>J</i> = 7.6 Hz, 1H), 7.27 (d, <i>J</i> = 8 Hz, 2H), 6.52 (t, <i>J</i> = 8 Hz, 2H), 4.51 (s, 2H), 3.96 (s, 3H), 1.51 (s, 9H).
29		440.1	¹ H NMR (400 MHz, CDCl ₃) δ 8.82 (d, <i>J</i> = 5.2 Hz, 1H), 8.20 (s, 1H), 8.09 (dd, <i>J</i> ₁ = 1.2 Hz, <i>J</i> ₂ = 6 Hz, 1H), 7.49 (m, 3H), 7.28 (m, 1H), 6.85 (m, 2H), 4.65 (s, 2H), 2.95 (s, 3H), 1.69 (s, 9H).
30		444.1	¹ H NMR (400 MHz, CDCl ₃) δ 9.24 (s, 1H), 8.84 (s, 2H), 7.55 (s, 1H), 7.47 (m, 3H), 6.52 (t, <i>J</i> = 7.6 Hz, 2H), 4.50 (s, 2H), 1.51 (s, 9H).

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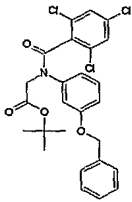
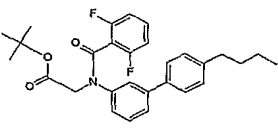
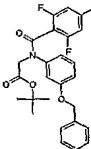
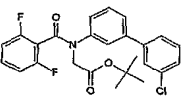
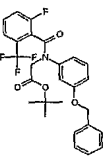
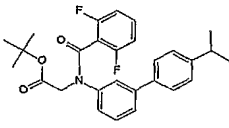
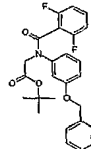
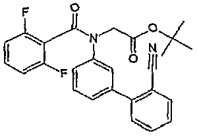
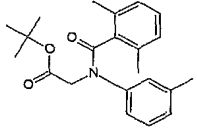
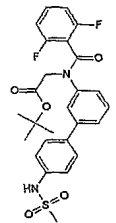
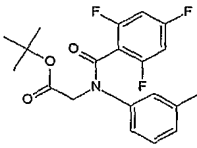
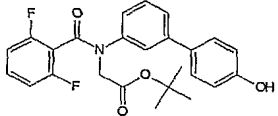
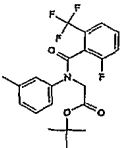
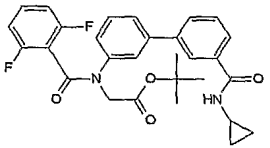
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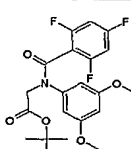
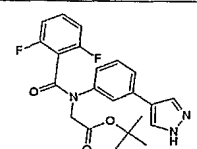
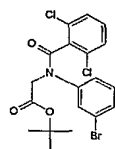
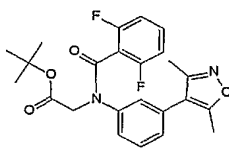
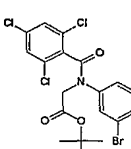
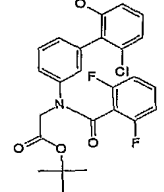
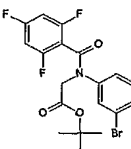
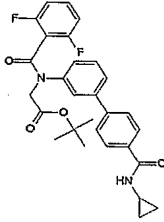
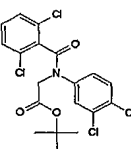
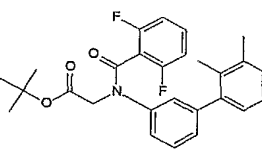
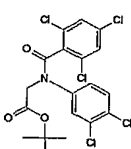
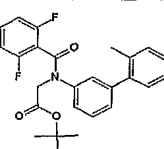
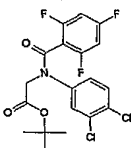
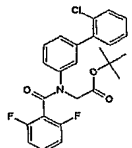
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Table 2

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
31		384.1 (M+23) ⁺	38		416.1 (M+23) ⁺
32		368.2	39		414.1 (M+23) ⁺
33		442.0	40		402.1 (M+23) ⁺
34		394.1	41		500.2
35		426.1	42		454.1
36		376.2	43		500.2
37		486.1	44		502.2 (M+23) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
45		520.0	52		480.2
46		472.1	53		458.1
47		504.1	54		466.2
48		454.1	55		449.1
49		354.2	56		461.1 (M-55) ⁺
50		380.1	57		440.1
51		412.1	58		507.3

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
59		362.2	66		455.1 (M-55) ⁺
60		414.0	67		479.2 (M-55) ⁺
61		374.2	68		454.1 (M-55) ⁺
62		448.0	69		425.2
63		400.1	70		426.2
64		432.1	71		454.2
65		474.0	72		495.2

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
73		426.1	80		414.1
74		458.0	81		443.2
75		491.9	82		488.1
76		444.0	83		507.2
77		448.0	84		452.2
78		481.9	85		437.9
79		434.0	86		458.1

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
87		466.0	93		603.2
88		398.1	94		440.2
89		380.1	95		478.2
90		438.1	96		428.1 (M-55) ⁺
91		472.0	97		423.1 (M-55) ⁺
92		424.2	98		423.1 (M-55) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
99		456.1	107		476.1 (M-55) ⁺
100		450.1	108		392.1
101		442.0	109		402.2 (M+23) ⁺
102		394.2	110		417.1
103		426.2	111		417.1
104		376.1	112		436.1 (M+23) ⁺
105		505.9	113		406.1
106		540.1	114		390.1

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
115		424.1	122		414.1 (M-55) ⁺
116		384.2	123		436.1 (M+23) ⁺
117		458.0	124		423.1
118		410.1	125		342.1 (M-55) ⁺
119		442.1	126		342.1 (M-55) ⁺
120		512.0	127		406.1
121		358.2	128		435.1

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
129		384.1	137		405.1
130		456.1	138		405.1
131		416.2	139		408.1
132		474.1	140		504.2 (M+23) ⁺
133		424.1	141		440.1 (M-55) ⁺
134		426.0	142		546.2 (M+23) ⁺
135		386.2	143		524.2
136		394.1	144		461.1 (M-55) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
145		428.0	153		482.1
146		388.1	154		481.2
147		396.1	155		495.2
148		402.9	156		523.3
149		400.1	157		523.3
150		398.2	158		523.3
151		452.1	159		467.2
152		472.0	160		521.2

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
161		432.0	168		557.2
162		437.1	169		559.2 (M+23) ⁺
163		458.1	170		495.2
164		430.1	171		532.2 (M+23) ⁺
165		418.1	172		504.2
166		415.1	173		472.2
167		396.1	174		468.2

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
175		414.2	182		518.2 (M+23) ⁺
176		433.1	183		468.2
177		416.1	184		482.2
178		432.1	185		518.2 (M+23) ⁺
179		402.1	186		440.2
180		481.0	187		492.1
181		480.0	188		416.1 (M-55) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
189		419.1	197		482.2 (M+23) ⁺
190		424.1	198		480.1 (M+23) ⁺
191		405.1	199		456.2
192		472.0	200		524.2 (M+23) ⁺
193		453.0	201		498.2 (M+23) ⁺
194		396.1	202		510.1 (M+23) ⁺
195		422.1	203		468.2
196		490.0	204		500.1 (M+23) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
205		408.1	213		460.2
206		382.1	214		437.9
207		440.1	215		478.2 (M+23) ⁺
208		412.1	216		478.2 (M+23) ⁺
209		414.1	217		470.1 (M-55) ⁺
210		442.0	218		490.2 (M+23) ⁺
211		414.1	219		510.2
212		440.1	220		424.3 (M-55) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
221		478.0	228		603.2
222		472.1	229		481.2 (M-55) ⁺
223		446.1	230		515.2
224		458.1	231		443.3 (M-55) ⁺
225		506.1	232		521.0
226		406.2	233		482.2
227		409.2	234		453.3 (M-55) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
235		457.1	243		539.1
236		512.1	244		496.2
237		526.2	245		494.2 (M+23) ⁺
238		396.1	246		443.1 (M-55) ⁺
239		372.1	247		498.1 (M+23) ⁺
240		416.0	248		482.1 (M+23) ⁺
241		416.1 (M+23) ⁺	249		479.0 (M-55) ⁺
242		406.0	250		464.1 (M+23) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
251		453.0	259		402.1 (M-55) ⁺
252		408.0	260		555.2
253		442.1	261		485.1
254		449.1	262		494.1 (M+23) ⁺
255		425.0 (M-56) ⁺	263		498.1 (M+23) ⁺
256		476.1 (M+23) ⁺	264		525.2
257		428.0	265		497.1 (M-55) ⁺
258		514.2	266		469.1 (M-55) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
267		449.1	275		443.1
268		444.1	276		508.1 (M+23) ⁺
269		444.1	277		450.0 (M-55) ⁺
270		537.2	278		513.2
271		508.1	279		473.1 (M-55) ⁺
272		502.0	280		500.1 (M+23) ⁺
273		442.1	281		512.2 (M+23) ⁺
274		490.1 (M+23) ⁺	282		526.1 (M+23) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
283		485.1 (M+23) ⁺	291		499.2
284		502.1	292		541.2
285		495.2	293		541.2
286		390.1	294		575.2
287		390.1	295		567.2
288		414.1	296		513.2
289		374.1	297		548.1 (M+23) ⁺
290		437.7	298		492.1 (M+23) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
299		435.1	307		473.2
300		406.0	308		494.1 (M+23) ⁺
301		408.1	309		548.1 (M+23) ⁺
302		352.1 (M-56) ⁺	310		528.1 (M+23) ⁺
303		432.1	311		446.1 (M-55) ⁺
304		392.1	312		476.1 (M-55) ⁺
305		456.0	313		508.1 (M+23) ⁺
306		456.0	314		432.0 (M-55) ⁺

Compound number	Structure	MS (m/z) (M+1) ⁺	Compound number	Structure	MS (m/z) (M+1) ⁺
315		480.0	321		455.1
316		440.0	322		460.1 (M-55) ⁺
317		416.1 (M+23) ⁺	323		530.1 (M+23) ⁺
318		428.1 (M+23) ⁺	324		458.1 (M-55) ⁺
319		416.1 (M+23) ⁺	325		414.1 (M-55) ⁺
320		446.1 (M-55) ⁺	326		493.0 (M+23) ⁺

Assay1 - Transcriptional Assay

[0075] Transfection assays are used to assess the ability of compounds of the invention to modulate the transcriptional activity of the LXRs. Briefly, expression vectors for chimeric proteins containing the DNA binding domain of yeast GAL4 fused to the ligand-binding domain (LBD) of either LXR α or LXR β are introduced via transient transfection into mammalian cells, together with a reporter plasmid where the luciferase gene is under the control of a GAL4 binding site. Upon exposure to an LXR modulator, LXR transcriptional activity varies, and this can be monitored by changes in luciferase

levels. If transfected cells are exposed to an LXR agonist, LXR-dependent transcriptional activity increases and luciferase levels rise.

[0076] 293T human embryonic kidney cells (8×10^6) are seeded in a 175cm^2 flask 2 days prior to the start of the experiment in 10% FBS, 1% Penicillin/Streptomycin/Fungizone, DMEM Media. The transfection mixture for chimeric proteins is prepared using GAL4-LXR LBD expression plasmid ($4\mu\text{g}$), UAS-luciferase reporter plasmid ($5\mu\text{g}$), Fugene (3:1 ratio; $27\mu\text{L}$) and serum-free media ($210\mu\text{L}$). The transfection mixture is incubated for 20 minutes at room temperature. The cells are harvested by washing with PBS (30mL) and then dissociated using trypsin (0.05% ; 3mL). The trypsin is inactivated by the addition of assay media (DMEM, lipoprotein-deficient fetal bovine serum (5%), statin (e.g. lovastatin $7.5\mu\text{M}$), and mevalonic acid ($100\mu\text{M}$)) (10mL). The cells are counted using a 1:10 dilution and the concentration of cells adjusted to $160,000\text{cells/mL}$. The cells are mixed with the transfection mixture (10mL of cells per $250\mu\text{L}$ of transfection mixture) and are further incubated for 30 minutes at room temperature with periodic mixing by inversion. Cells ($50\mu\text{L/well}$) are then plated into 384 white, solid-bottom, TC-treated plates. The cells are further incubated at 37°C , $5.0\% \text{CO}_2$ for 24 hours. A 12-point series of dilutions (half-log serial dilutions) are prepared for each test compound in DMSO with a starting concentration of compound of $1\mu\text{M}$. Test compound (500nL) is added to each well of cells in the assay plate and the cells are incubated at 37°C , $5.0\% \text{CO}_2$ for 24 hours. The cell lysis/luciferase assay buffer Bright-GloTM (25% ; $25\mu\text{L}$; Promega), is added to each well. After a further incubation for 5 minutes at room temperature, the luciferase activity is measured.

[0077] Raw luminescence values are normalized by dividing them by the value of the DMSO control present on each plate. Normalized data is visualized using XLfit3 and dose-response curves are fitted using a 4-parameter logistic model or sigmoidal single-site dose-response equation (equation 205 in XLfit3.05). EC50 is defined as the concentration at which the compound elicits a response that is half way between the maximum and minimum values. Relative efficacy (or percent efficacy) is calculated by comparison of the response elicited by the compound with the maximum value obtained

for the known LXR modulator (3-{3-[(2-Chloro-3-trifluoromethyl-benzyl)-(2,2-diphenyl-ethyl)-amino]-propoxy}-phenyl)-acetic acid.

Assay2 - FRET Co-activator Recruitment Assay

5 [0078] A FRET assay is used to assess the ability of a compound of the invention to bind directly to the LXR ligand-binding domain (LBD) and promote the recruitment of proteins that potentiate the transcriptional activity of LXRs (e.g. co-activators). This cell-free assay uses a recombinant fusion protein composed of the LXR LBD and a tag (e.g. GST, His, FLAG) that simplifies its purification, and a synthetic biotinylated peptide derived from the nuclear receptor interacting domain of a transcriptional co-activator protein, such as steroid
10 receptor co-activator 1 (SRC-1). In one format, the tagged LBD fusion protein can be labeled using an antibody against the LBD tag coupled to europium (e.g. EU-labeled anti-GST antibody), and the co-activator peptide can be labeled with allophycocyanin (APC) coupled to streptavidin. In the presence of an agonist for LXR, the co-activator peptide is recruited to the LXR LBD, bringing the EU and APC moieties in close proximity. Upon excitation of the
15 complex with light at 340nm, EU absorbs and transfers energy to the APC moiety resulting in emission at 665 nm. If there is no energy transfer (indicating lack of EU-APC proximity), EU emits at 615nm. Thus the ratio of the 665 to 615nm light emitted gives an indication of the strength of co-activator peptide recruitment, and thus of agonist binding to the LXR LBD.

[0079] Fusion proteins, amino acids 205-447 (Genbank NM_005693) for LXR α and
20 amino acids 203-461 (NM_007121 for β) for LXR β , were cloned in-frame at the SalI and NotI sites of pGEX4T-3 (27-4583-03 Amersham Pharmacia Biotech). A biotinylated peptide sequence was derived from SRC-1 (amino acids 676 to 700): biotin-CPSSHSSLTERHKILHRLQLQEGSPSC-OH.

[0080] A master mix is prepared (5nM GST-LXR-LBD, 5nM Biotinylated SRC-1
25 peptide, 10nM APC-Streptavidin (Prozyme Phycolink streptavidin APC, PJ25S), and 5nM MEU-Anti-GST Antibody) in FRET buffer (50mM Tris pH 7.5, 50mM KCl 1mM DTT, 0.1% BSA). To each well of a 384 well plate, 20 μ L of this master mix is added. Final FRET reaction: 5nM fusion protein, 5nM SRC-1 peptide, 10nM APC-Streptavidin, 5nM EU-Anti-GST Antibody (PerkinElmer AD0064). Test compounds are diluted in half-log, 12-point
30 serial dilutions in DMSO, starting at 1mM and 100nL of compound is transferred to the

master mix for a final concentration of 5 μ M-28pM in the assay wells. Plates are incubated at room temperature for 3 hours and fluorescence resonance energy transfer read. Results are expressed as the ratio of APC fluorescence to EU fluorescence times one thousand.

[0081] The ratio of 665nm to 615nm is multiplied by a factor of 1000 to simplify data analysis. DMSO values are subtracted from ratios to account for background. Data is visualized using XLfit3 and dose-response curves are fitted using a 4-parameter logistic model or sigmoidal single-site dose-response equation (equation 205 in XLfit3.05). EC50 is defined as the concentration at which the compound elicits a response that is half way between the maximum and minimum values. Relative efficacy (or percent efficacy) is calculated by comparison of the response elicited by the compound with the maximum value obtained for a reference LXR modulator.

[0082] Compounds of Formula I, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example, as indicated by the *in vitro* tests described in this application. Compounds of the invention have EC50 between 0.001 μ M and 1.5 μ M and %Efficacy between 20% and 150% in the transcriptional assay for LXR β . It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.